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Blood cadmium concentrations in the general population of Umbria, Central Italy

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Abstract

The aims of this study were (a) to assess blood cadmium (B-Cd) concentrations and to establish a tentative reference interval; (b) to identify significant determinants of B-Cd, in a population from Umbria, Central Italy, which was not occupationally exposed to cadmium (Cd). Four hundred and thirty-four healthy blood-donors volunteered to answer a questionnaire and provide a blood sample for B-Cd analysis, which was performed by graphite furnace atomic absorption spectrophotometry. Blood Cd concentrations ranged from non-detectable values, i.e. below 0.1 μg/l up to 3.4 μg/l and were not normally distributed. The median values and the 95th percentiles were 0.7 and 2.0 μg/l, respectively. Concentrations of B-Cd were more than double in smokers than in non-smokers, median values being 1.1 μg/l and 0.5 μg/l, respectively. In current smokers, B-Cd values correlated with the number of cigarettes smoked daily ($r_s = 0.40$, $P = 0.0001$) and with the cumulative exposure to cigarette smoke ($r_s = 0.35$, $P = 0.0001$). Concentrations of B-Cd correlated with age in the non-smokers, but not in the smokers and were significantly higher in women than in men only in the non-smokers. Both in smokers and non-smokers, B-Cd concentrations were similar in subjects living in urban or in rural areas. In the whole study population the lower and the upper tentative reference limit were < 0.1 and 2.2 μg/l, respectively, as computed by a non-parametric rank-based method. The upper limit was approximately double in smokers than in non-smokers (3.1 μg/l and 1.6 μg/l, respectively). Our results show that B-Cd concentrations in a general population from Umbria are in the range reported for general populations in Northern Italy and other European Countries. Smoking was the strongest determinant of B-Cd concentrations and age had a lesser effect.

Keywords: Cadmium; Blood; Environmental exposure; Reference intervals; General population

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1. Introduction

Cadmium (Cd) is a heavy metal which pollutes the environment and may cause toxicity in humans.

Toxic effects due to long-term occupational and/or environmental exposure have recently been reviewed (Järup et al., 1998). The kidney is the target organ and current evidence is that early signs of proximal tubular damage (i.e. microproteinuria) are detectable in a low percentage of environmentally exposed populations in industrialized countries (Buchet et al., 1990; Bernard et al., 1992; Järup et al., 1998). Moreover, Cd is a carcinogen (lung neoplasm) in occupationally exposed populations according to the International Agency for Research on Cancer (group I) (IARC, 1993), and a probable human carcinogen according to the European Community (category 2; annex 1 to Directive 67/548/EEC).

In non-occupationally exposed populations, the major sources of environmental exposure to, and intake of, Cd are diet and smoking. Cadmium is contained in many foodstuffs and the average daily intake of Cd in European Countries and in the United States has been estimated at 10–30 μg (WHO, 1987; Herber et al., 1997). Each cigarette contains 1–2 μg of Cd, approximately 10% of which is inhaled, and 5% absorbed (Elinder et al., 1983; Friberg et al., 1986). A minor source of environmental exposure to Cd is ambient air (WHO, 1987; Vahter et al., 1991).

Blood Cd (B-Cd) is a biomarker of environmental and occupational Cd exposure. Under conditions of moderate exposure, B-Cd reflects recent Cd exposure (weeks or months), while in subjects with long-term exposure and in those who have accumulated large amounts of Cd, the total Cd body-burden may influence B-Cd level (WHO, 1992; Lauwerys and Hoet, 1993).

Reference values for B-Cd may be defined as the B-Cd concentration interval in healthy individuals living in a specific geographical area, with a defined life style and eating, drinking and smoking habits, with a defined age and sex, who are not professionally exposed to the metal (Brune et al., 1991).

Several studies have reported B-Cd reference values for populations living in America, Asia and several European countries (Friberg and Vahter, 1983; Watanabe et al., 1989; Alessio et al., 1994; Benedetti et al., 1994; Watanabe et al., 1996; Herber et al., 1997; Zhang et al., 1997). Data from Germany, Belgium, Sweden, Yugoslavia, England and Northern Italy (a heavily industrialized area) are available (Brockhaus et al., 1983; Castoldi et al., 1983; Friberg and Vahter, 1983; Pocock et al., 1988; Alessio et al., 1990; Maranelli et al., 1990; Minoia et al., 1990; Staessen et al., 1990; Sartor et al., 1992; Roggi et al., 1995; Järup et al., 1998), but there is no data on the population of Central Italy which is a less industrialized area than the North.

Thus, the aims of our study were to describe the distribution of reference B-Cd concentrations in a population from Central Italy which was not occupationally exposed to the metal and to assess the determinants of B-Cd concentrations.

2. Subjects and methods

2.1. Study population

This study was carried out between September 1992 and April 1993.

Male and female blood donors residing in Umbria, a Region of Central Italy with a population of approximately 800 000 answered a questionnaire administered by two occupational health physicians.

The questionnaire investigated factors which might cause exposure to, and absorption of, Cd, and which might modify B-Cd concentrations, i.e. age, sex, smoking habit, residential area, occupation, hobbies (Herber et al., 1997). Questions about current disease and medication were also included.

Exclusion criteria were:

- aged under 18 or over 65;
- occupational- or hobby-related exposure to Cd;
- current diseases, e.g. liver, kidney, haematological, cardiovascular or metabolic diseases.

In the study period 444 subjects were invited to participate. Three were excluded on the basis of age and 7 because of probable occupational exposure to Cd.

The final study population was made up of 434 subjects (208 females, 47.9%; 226 males, 52.1%). Their mean age was 37.7 (S.D. 10.4) years, range 18–64 years. One hundred and sixty-three subjects were current smokers, with a median consumption of 15 cigarettes/day, 94 were ex-smokers and 177 had never smoked. Fifty-three subjects (12.2%) lived in a rural area and 381 (87.8%) in an urban environment. All subjects were Caucasians.

2.2. *Blood-Cd sampling and analysis*

Blood samples using a vacutainer BD test tube containing Sodium-heparin with a stainless steel needle were drawn from all subjects. Samples were stored at 4°C for a maximum of 72 h before analysis. All B-Cd measurements were performed using an atomic absorption spectrophotometer, equipped with a Zeeman-effect background correction system (Spectra AA 300, Varian Techtron, Victoria, Australia) at a 228.8 nm wave length.

Blood samples were diluted 1:10 in a 0.05% ammonium-sulphate solution and 0.2% Triton X-100 (Merck, Darmstadt, Germany). Ten μl were injected into the graphite furnace.

Calibration was performed adding fixed amounts of Cd to human blood samples. The detection limit (NIOSH, 1994) was 0.1 μg/l.

Within-run precision was assessed by 10 assays of Cd levels in two blood samples (mean values 0.5 and 2.9 μg/l). The coefficients of variation were 12.9 and 2.0%, respectively. Between-run precision was assessed by 12 assays of Cd concentration in two samples (mean values 0.5 and 2.9 μg/l). The coefficients of variation were 18.8 and 4.5%, respectively.

All materials used for collecting, storing and analysing blood samples were Cd-free at the release tests, which were performed by placing materials in a nitric acid solution.

Throughout the study period, quality of B-Cd analysis was controlled by analysing two samples of certified standard reference materials (Community Bureau of Reference, Brussels, Belgium; samples no. 194 and 195, with a certified Cd concentration of 0.5 (S.D. 0.1) μg/l and 5.37 (0.24) μg/l) for each 8 samples from study subjects. Furthermore our laboratory took part in the 'METOS' inter-laboratory quality control program, organized by the Istituto Superiore di Sanità, Italian Ministry of Health, Rome (Menditto et al., 1996). Over the course of the study our laboratory always provided B-Cd results within the acceptability limits of the target values (No. 31 determinations).

3. Results

Blood Cd concentrations ranged from non-detectable values, i.e. below 0.1 μg/l (4.8% of the subjects; 20 non-smokers and one smoker) up to 3.4 μg/l. For the statistical analysis, the value of 0.05 μg/l was attributed to B-Cd concentrations below the detection limit.

The distribution of B-Cd concentrations was positively skewed and did not fit a normal distribution for either the whole study population (Fig. 1a) or after dividing subjects into current non-smokers (i.e. ex-smokers and never-smokers) and smokers (Kolmogorov–Smirnov test, $P = 0.0001$ for each data distribution). Even after log-transformation, B-Cd values were not normally distributed ($P = 0.0001$) (Fig. 1b). The 25th, 50th, 75th, and 95th percentiles of data distribution were 0.4, 0.7, 1.1 and 2.0 μg/l, respectively.

Concentrations of B-Cd were more than double in smokers than in current non-smokers, median values being 1.1 μg/l and 0.5 μg/l, respectively (Wilcoxon rank sum test, $P = 0.0001$) (Table 1, Fig. 2). In smokers, B-Cd values correlated with the number of cigarettes smoked daily and with the cumulative exposure to cigarette smoke, as assessed by computation of pack-years ($r_s = 0.40$, $P = 0.0001$; $r_s = 0.35$, $P = 0.0001$, respectively). Concentrations of B-Cd in never-smokers were not significantly different from those in ex-smokers (Table 1).

Concentrations of B-Cd correlated with age in the current non-smokers but not in the smokers ($r_s = 0.15$, $P = 0.014$; $r_s = 0.07$, $P = 0.35$, respectively). Concentrations were significantly higher in

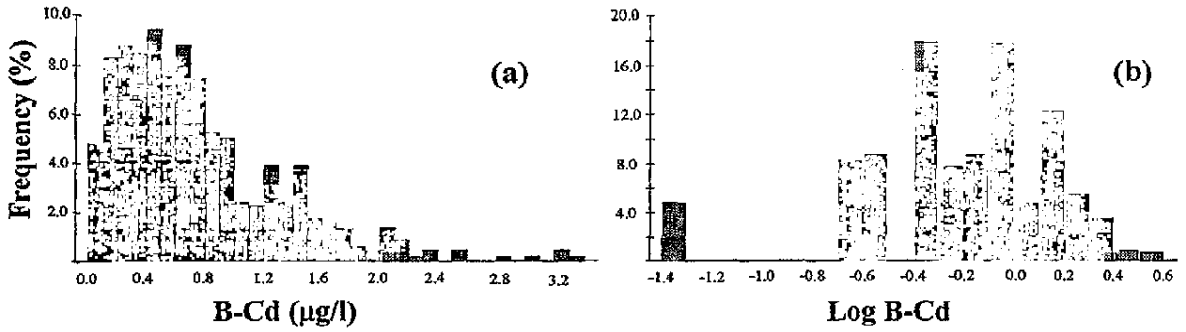

Fig. 1. Frequency distribution of blood cadmium (a) and log-transformed blood cadmium (b) concentrations in the study population (No. 434).

women than in men only in the current non-smokers ($P = 0.017$) (Table 1). Both in smokers and non-smokers, B-Cd concentrations were similar in subjects living in urban or in rural areas (Table 1).

Multiple regression analysis was performed on raw and log-transformed B-Cd data to identify determinants of B-Cd levels. The models accounted for up to 29% of the total variance. Current smoking was by far the most important determinant and only age significantly contributed to each model, at a much lower degree (Table 2).

Tentative reference intervals were computed for the whole population and for current non-smokers and smokers separately by a non-parametric rank-based method (IFCC, 1987). The lower and the upper reference limits were set equal to the B-Cd concentrations corresponding to the rank number of the 0.025 and 0.975 fractiles, respectively. In the whole study population the lower and the upper limit were < 0.1 and 2.2 μg/l, respectively. The upper limit was approximately double in smokers than in non-smokers (Table 3).

4. Discussion

We measured B-Cd concentrations in a non-occupationally exposed population from Central Italy and showed that human environmental exposure to Cd is widespread and relatively low in Umbria. In fact, B-Cd was dosable in almost all subjects and average B-Cd concentrations

Table 1
Blood Cadmium levels (μg/l) in relation to smoking habit, gender and residential area

	Non-smokers						Smokers					
	No.	Median	5° pct	25° pct	75° pct	95°pct	No.	Median	5° pct	25° pct	75° pct	95°pct
Total population	271	0.5	< 0.1	0.3	0.7	1.4	163	1.1	0.3	0.8	1.5	2.3
Smoking habit												
Ex-smokers	94	0.5	< 0.1	0.3	0.8	1.4						
Never smokers	177	0.5	< 0.1	0.3	0.7	1.3						
Gender												
Males	130	0.4	< 0.1	0.3	0.6	1.3	96	1.2	0.3	0.8	1.6	2.4
Females	141	0.5	0.2	0.3	0.8	1.5	67	1.0	0.3	0.7	1.5	2.3
Residence												
Rural	35	0.4	< 0.1	0.2	0.6	1.7	18	1.35	0.2	1.0	1.7	2.4
Urban	236	0.5	< 0.1	0.3	0.7	1.3	144	1.05	0.3	0.7	1.5	2.2

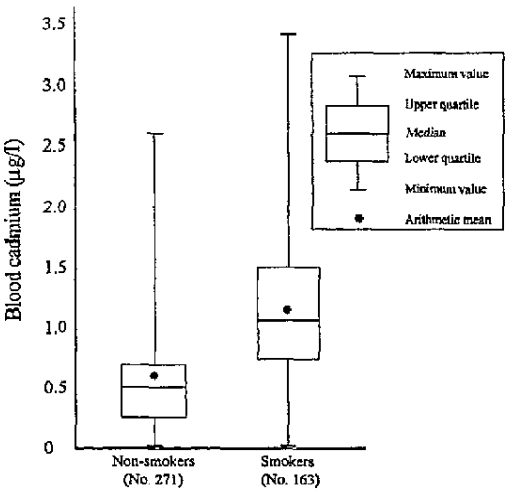

Fig. 2. Box and whisker plots of blood cadmium concentrations in smokers and non-smokers.

(median: 0.7 μg/l) are in the range of the values reported for the general populations of Northern Italy (range of G.M. 0.5–0.7 μg/l) (Castoldi et al., 1983; Alessio et al., 1990; Maranelli et al., 1990; Roggi et al., 1995), Belgium, Sweden and Germany (range 0.5–1.2 μg/l) (Brockhaus et al., 1983; Friberg and Vahter, 1983; Sartor et al., 1992; Järup et al., 1998). Higher exposure has been reported in England (Pocock et al., 1988) and in countries outside Europe, particularly in Japan (Watanabe et al., 1983, 1985). In a recent study on non-smoking Japanese women the G.M. of B-Cd concentrations was 2.0 μg/l (Watanabe et al., 1996), which was attributed to dietary Cd intake, and in particular to the consumption of highly contaminated rice (Watanabe et al., 1985, 1996).

Blood-Cd concentrations may be influenced by several factors, i.e. diet, smoking, age, sex, area of residence, occupation, hobbies and medication (Herber et al., 1997). Our exclusion criteria ensured no subject had been exposed to Cd through his job or hobbies and no one was affected by metabolic, cardiovascular, respiratory and renal diseases requiring pharmacological therapy. Thus in order to identify remaining determinants of B-Cd concentrations, we performed both non parametric and parametric multivariate statistical analysis. Even though the coefficients of multi-

Table 2
Determinants of blood cadmium and log-transformed blood cadmium concentrations as assessed by multiple regression analysis

Variable	Parameter					
	Normal model ($r^2 = 0.29$)			Log model ($r^2 = 0.25$)		
	β	t-value	P-value	β	t-value	P-value
Smoking habit	0.635	12.72	0.0001	0.375	11.52	0.0001
Age	0.007	3.02	0.003	0.005	3.11	0.002
Sex	0.049	1.02	0.310	0.068	2.16	0.031
Residential area	0.063	0.85	0.397	−0.004	−0.09	0.932

Variable coding: Smoking habit: 0 = non-smoker; 1 = smoker; Sex: 0 = male; 1 = female; residential area: 0 = urban; 1 = rural.

Table 3
Tentative reference intervals for blood cadmium (μg/l) in non-occupationally exposed populations in Italy

Population	Non-smokers		Smokers	
	No.	Tentative reference intervals	No.	Tentative reference intervals
Umbria (this study)	271	<0.1–1.6	163	0.2–3.1
Pavia[a]	389	0.14–1.27	125	0.24–2.68
Italian case list[b]	835	0.09–1.6	444	0.23–2.73

[a]From: Roggi et al., 1995.
[b]From: Alessio et al., 1994 and Roggi et al., 1995 (population samples collected in Brescia, Verona and Milan, Northern Italy).

variate analysis might be biased because of the high departure of B-Cd concentrations from normality in our population, results of parametric and non-parametric analysis lead to similar conclusions.

Our results show smoking significantly increases B-Cd concentrations which were on average doubled in smokers compared with non-smokers. This increase depends mostly on current consumption of cigarettes and, possibly to a lesser extent, on the lifetime cumulative amount. This finding concurs with other reports, showing B-Cd concentrations are 2–5 times higher in smokers than in non-smokers (Brockhaus et al., 1983; Friberg and Vahter, 1983; Alessio et al., 1994; Roggi et al., 1995; Järup et al., 1998). Unusually high B-Cd levels have been reported for urban and rural smokers from Quebec, Canada, who have mean B-Cd approximately 14 times higher than non-smokers (urban population: 46.1 μg/l vs. 3.3 μg/l; rural population: 40.0 μg/l vs. 2.7 μg/l). These high B-Cd values in smokers can be explained only partially by the higher Cd content in Canadian-made cigarettes as compared with cigarettes produced in other countries (Benedetti et al., 1994). On the contrary B-Cd concentrations were almost similar in Indian smokers and non-smokers (Friberg and Vahter, 1983).

In our population, B-Cd slightly increases with age. A similar increase has been previously reported (Alessio et al., 1993; Roggi et al., 1995), and is related to Cd accumulation of in the body, particularly in the kidney and liver (Friberg et al., 1986). The biological half-life of Cd in these tissues ranges between 10–30 years and 4.7–9.7 years, respectively (Kjellstrom et al., 1978; Ellis et al., 1985).

When the smoking habit and age had been accounted for, we found sex and area of residence had little, if any, effect on B-Cd concentrations, thus confirming other reports (Staessen et al., 1990; Roggi et al., 1995). On the other hand B-Cd has been reported to be higher in non-smoking Swedish women than non-smoking men (Järup et al., 1998), but in Norther Italy men had higher values (Alessio et al., 1993). In the face of these conflicting results it is difficult to came to any definitive conclusion.

We could not quantify the extent to which dietary Cd intake contributes to B-Cd concentration. On the basis of the range of B-Cd concentrations in our non-smoking population, we presume that differences in dietary habits and other nutritional factors may explain in part inter-individual difference in B-Cd concentrations in our population (Järup et al., 1998).

In our population, the distribution of B-Cd concentrations did not fit the normal distribution even after log-transformation. This finding contrasts with the assumption that B-Cd concentrations in the general populations are log-normally distributed and that the G.M. and G.S.D. are appropriate statistics to estimate reference limits (Alessio et al., 1994). Thus, we chose a distribution-free non-parametric method for our estimates of reference limits (IFCC, 1987).

We found that the upper limit for smokers is slightly higher than reported for other areas of Italy (Table 3). Furthermore, it is worth noting this limit is approximately twice as high as in non-smokers, suggesting smoking must be taken into account when estimating reference values (Table 3).

In a recent critical evaluation of studies on B-Cd in general populations, emphasis was placed on the need for checking the quality of B-Cd analytical methods (Herber et al., 1997). In our study we took care of pre-analytical and analytical factors which might interfere with B-Cd measurements, e.g. by using Cd-free materials for blood sample collection and analysis, by using certified reference standard material, and by participating in an inter-laboratory quality control program. We hope our results will be useful for: (i) monitoring the course of Cd exposure over time; (ii) evaluating data from biological monitoring of Cd-exposed workers; (iii) determining the B-Cd threshold concentration for early toxic effects; and (iv) future meta-analysis of B-Cd concentrations in the general populations.

In conclusion, B-Cd levels in a population living in Umbria, Central Italy, which was not occupationally exposed to Cd were similar to those found in other European countries as well as in the more industrialized area of Northern Italy. Smoking was the strongest determinant of B-Cd

concentrations and age had a lesser, but significant effect.

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